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Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate

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The risk of an adverse outcome to pregnancy is increased in women with epilepsy. This is partly attributable to antiepileptic drugs. Guidelines for the management of pregnancy in women with epilepsy generally advise against polytherapy but make no distinction between the risks of different drugs. Several recent studies have however shown greater risk of adverse outcome in offspring exposed to sodium valproate *in utero*, particularly at higher doses. The outcome of pregnancy was monitored to identify antiepileptic drug treatment associated with a poor outcome in a mainly prospective study of women attending an outpatient clinic. From January 1990 to December 1999 all 69 pregnancies in women referred to the clinic were monitored. Drug treatments and other risk factors were recorded. In each child dysmorphic features, developmental delay and structural anomalies were assessed and graded. Data were analysed for drug- and dosage-dependent differences in outcome. In each assessment area a positive association between adverse outcome and dose was found for sodium valproate but not for carbamazepine. Severe adverse outcomes were found only in children exposed to sodium valproate at maternal doses above 1000 mg per day.

Key words: epilepsy; pregnancy; adverse outcome; valproate; carbamazepine.

INTRODUCTION

The risk of an adverse outcome to pregnancy is greater in women with epilepsy than in the general population[1]. This is partly attributable to antiepileptic drug treatment. Guidelines for the management of pregnancy in women with epilepsy[1–4] consistently advise against polytherapy but generally make no distinction between the risks of different antiepileptic drugs (AEDs) when given as monotherapy.

Recently however several studies have shown a greater risk of adverse outcome in offspring exposed to higher doses of sodium valproate *in utero* (see Discussion) and the Royal College of Physicians of London[2] has advised the avoidance of 'high daily doses of valproate, e.g. more than 1000 mg per day' before conception in the interest of risk reduction. Similarly the Epilim data sheet[5] from 1998 onwards acknowledges that 'abnormal pregnancy outcome tends to be associated with higher total daily dosage'.

We report here the results of monitoring pregnancies prospectively over a 10-year period in women attending an epilepsy clinic at a teaching hospital. Although patient numbers were not large they did permit comparison between carbamazepine and sodium valproate, when each was given as monotherapy. The worst affected offspring were those exposed to higher doses of the latter; a small number of these cases were assessed retrospectively.

PATIENTS AND METHODS

Forty-five mothers, pregnant between January 1990 and December 1999, attended the Epilepsy Clinic at the Manchester Royal Infirmary. Twenty-six had

focal epilepsy (F), 17 had idiopathic generalised epilepsy (IG) and in 2 the epilepsy was unclassified (UC). Maternal epilepsy syndrome diagnoses were based on seizure history including description by a witness, EEG and brain imaging; they are indicated in Tables 2–4.

In all but four instances the pregnancies were assessed prospectively. Most women were under the care of the clinic before conception but about one-third were already pregnant at referral. Four women were referred for advice after bad outcomes to earlier pregnancies; these were assessed in retrospect and compared with the outcome of subsequent pregnancies after drug treatment changes. The study included every pregnancy known to the medical/nursing staff in women attending the clinic; there were no exclusions.

Children

Of 69 pregnancies, 10 were lost. Fifty-nine babies (25 male, 34 female) were born but 2 mothers with idiopathic generalised epilepsy (IG) refused assessment of their 3 children (1 exposed to sodium valproate, 2 to polytherapy) and 56 children were assessed by a consultant clinical geneticist. Age at assessment ranged from 4 months to 10 years. No specific genetic syndrome was identified in any of the children. The assessors of the children had no direct involvement with the clinical care of the mother but no steps were taken to conceal her history and drug treatment from the assessor.

Assessment

The condition of each child was assessed in three areas—dysmorphic features, developmental delay and structural anomalies. In each area the severity of adverse outcome was graded on a discontinuous scale—0 none, 1 mild, 2 moderate, 3 severe. The basis of this grading is shown in Table 1.

Dysmorphic features (prominent midline ridge to forehead, wide set eyes, epicanthic folds, flat nasal bridge, upturned nose, flat philtrum, dysplastic ears, down turned mouth, hypoplastic nails, overlapping digits) were listed and counted; the more numerous the features, the more severe the degree of dysmorphism.

Developmental delay was rated as mild if the child did attain normal milestones *albeit* at an older age than usual. Developmental delay was moderate if special educational needs had been identified and extra help was needed for the child to acquire skills; there was often a formal Statement of Special Needs. Delay was rated as severe when there was little or no speech and the child remained dependent on others for most aspects of daily living.

Structural anomalies were rated as mild (for example capillary naevus or inguinal hernia) when they produced no disability. Anomalies were moderate (talipes, hip dislocation) when intervention was needed to prevent physical disability. They were rated as severe when there was failure of embryonic fusion (cardiac septal defect, cleft hand, cleft palate, coloboma of the iris, hypospadias, spina bifida) or agenesis (radial ray deficiency). Surgical treatment was often needed within this group.

There was no control group of mothers who had no history of epilepsy but within the population of women with epilepsy comparisons were made between different treatment groups (sodium valproate monotherapy, carbamazepine monotherapy and polytherapy). Differences between valproate and carbamazepine in the distribution of drug doses were assessed by variance ratio. Since the severity of adverse outcome (Table 1) was not a continuous measure, the strength of an association between adverse outcome and drug dose for example was assessed using the Spearman rank correlation coefficient[6].

Table 1: Grading of an adverse outcome: each child was assessed in three areas[a].

Grade	Dysmorphic features	Developmental delay	Structural anomalies
0	None	None	None
1: Mild	1–3	Milestones attained after a delay	Minor anomaly but no disability, e.g. inguinal hernia
2: Moderate	4–6	Mild learning difficulty special educational needs	Minor anomaly with disability, e.g. talipes
3: Severe	>6	Moderate to severe learning difficulty	Major anomaly, e.g. neural tube defect cleft palate, coloboma

Dysmorphic features included prominent midline ridge to forehead, wide set eyes, epicanthic folds, flat nasal bridge, upturned nose, flat philtrum, dysplastic ears, down turned mouth, hypoplastic nails, overlapping digits. The score in this assessment area was the number of features identified.

[a] The severity of adverse features was graded on a discontinuous scale according to the criteria shown.

RESULTS

In 69 pregnancies antiepileptic drugs were prescribed, as follows:

no drug	1 pregnancy in a woman with partial seizures only
monotherapy	Sodium valproate (VPS), 23 pregnancies in 14 women (IG/F/UC = 9/4/1) Carbamazepine (CBZ), 18 pregnancies in 13 women (IG/F/UC = 0/12/1) Phenytoin (PHT), 7 pregnancies in 3 women (IG/F/UC = 0/3/0) Lamotrigine (LTG), 4 pregnancies in 3 women (IG/F/UC = 1/2/0) Ethosuximide (ESM), 1 pregnancy in a woman with IG epilepsy
polytherapy	Combined AED including the above, 15 pregnancies in 12 women (IG/F/UC = 6/6/0)

The total number of women listed above (47) exceeds the 45 stated earlier because 2 women who were switched from VPS to alternative treatment before a subsequent pregnancy each appear twice in different drug treatment groups.

Ten drug-exposed foetuses were lost—one ectopic pregnancy, five spontaneous miscarriages at 5, 8, 11, 12, and 19 weeks, one intrauterine death at 26 weeks and three terminations because of spina bifida.

The assessments of the 56 children and the three cases of spina bifida are summarised in Fig. 1a. Dysmorphic features were found in more than half the children and there was some evidence of developmental delay in about one-quarter. Structural anomalies were found in about one-third of offspring. In each area of assessment the adverse features were usually mild but in about 10% they were moderate or severe. Delayed development was associated with dysmorphic features (Spearman rank correlation coefficient 0.38, $P < 0.01$, $N = 56$) but not with structural anomalies (rank correlation coefficient 0.08, $P = 0.57$, $N = 56$).

Folic acid at 5.0 mg per day was taken before conception by 24 women and at 0.4 mg per day by 3 women. There was a significant negative correlation with the dose of folic acid for structural anomalies (Spearman rank correlation coefficient -0.263, $P = 0.04$, $N = 59$) but not for dysmorphic features ($P = 0.55$, $N = 56$) or delayed development ($P = 0.49$, $N = 56$).

Monotherapy with sodium valproate

The daily dose of VPS prescribed before conception is shown in Table 2; it ranged widely from 200 to 3000 mg (mean ± SD 1236 ± 771, coefficient of variation 0.623, $N = 22$). One woman with myoclonic epilepsy (case 41(i)) prescribed 3000 mg per day, had no detectable VPS in plasma twice during pregnancy. Plasma VPS was not measured in every patient however.

The outcomes of individual pregnancies in the three assessment areas are shown in Table 2. A moderate or severe adverse outcome in at least one assessment area was found in eight offspring.

In each assessment area a positive association was found between adverse outcome and VPS dose (Table 5). The significance was borderline for developmental delay but high for the other two areas. At doses below 1000 mg per day adverse features were absent or mild but at higher doses moderate or severe adverse features were found in one area of assessment at least, in half the children.

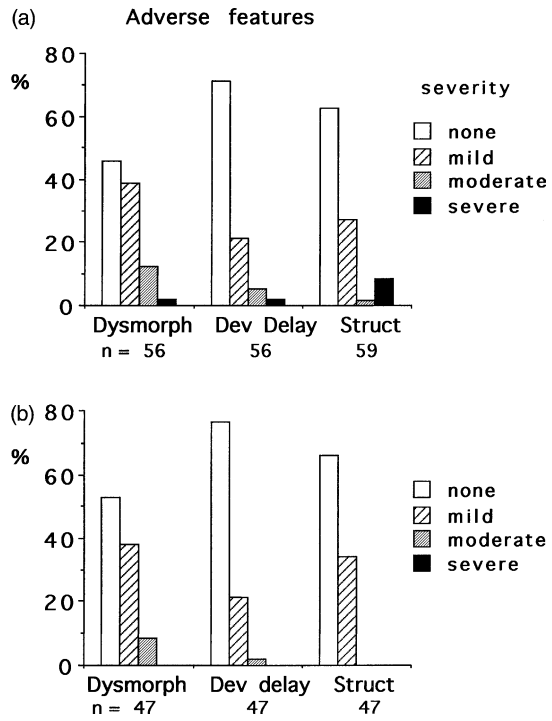

Fig. 1: Adverse features in the offspring of mothers with epilepsy: this shows the proportion (%) of the offspring in whom dysmorphic features (Dysmorph), developmental delay (Dev Delay) and structural anomalies (Struct) were found. Severity was graded as shown in Table 1. The total group (*a*) includes three cases of spina bifida, where termination of pregnancy restricted the assessment to the structural anomaly. The effect of excluding the 12 offspring exposed to maternal doses of sodium valproate greater than 1000 mg per day (in mono- or polytherapy) is shown in (*b*) moderate adverse features were reduced and severe adverse features were removed.

Table 2: Dose of sodium valproate taken by the mother at conception and severity of the adverse features observed in the child.

	Dose (mg per day)	Dysmorphic features	Developmental delay	Structural anomalies
Prospective cases				
2 F (ii)m	0	0	0	0
14 IG (ii)f	200	1	0	1
14 IG (iii)f	200	0	0	0
14 IG (i)	300	–	–	– (M)
6 IG (ii)f	400	0	0	0
33 IG (i)f	600	1	0	0
5 IG (i)m	600	0	1	0
5 IG (ii)m	600	0	1	1
28 IG (i)f	800	1	0	0
7 F (ii)f	800	1	0	1
13 IG (ii)f	1000	2	1	0
13 IG (i)f	1200	2	1	0
16 IG (ii)f	1200	0	0	0
16 IG (i)f	1400	1	0	0
7 F (i)	1600			– (M)
15 UC (i)m	1800	2	2	3
41 IG (i)f	3000	1	0	0
Retrospective cases				
6 IG (i)f	1400	1	2	0
10 F (i)	1600	–	–	3 (T)
11 F (i)	2000	–	–	3 (T)
11 F (ii)	2000	–	–	– (M)
11 F (i)f	2000	2	1	2
2 F (i)m	2500	3	3	3

Mother—study acquisition number 2–41; epilepsy syndrome F: focal, IG: idiopathic generalised, UC: unclassified. Child—number of pregnancy (i)–(iii); m/f: gender; adverse features 0: none, 1: mild, 2: moderate, 3: severe, (M): miscarriage, (T): termination.

Four women on VPS were referred for advice about medication before a future pregnancy; they each had adverse outcomes to earlier pregnancies on doses of 1400–2500 mg per day (retrospective cases, Table 2). After withdrawal of AED, reduction of VPS dose or transfer to CBZ, three of these women conceived again with a normal outcome (cases 2(ii) and 6(ii), Table 2; case 10(ii), Table 3) showing that the same parents could produce normal children in the absence of a high dose of VPS.

Monotherapy with carbamazepine

The daily dose of CBZ prescribed before conception is shown in Table 3; it ranged from 400 to 1200 mg

Table 3: Dose of carbamazepine taken by the mother at conception and severity of the adverse features observed in the child.

	Dose (mg per day)	Dysmorphic features	Developmental delay	Structural anomalies
18 F (i)m	400	1	0	0
39 UC (i)f	400	0	0	0
29 F (i)f	600	0	1	0
29 F (ii)m	600	1	0	1
24 F (ii)f	600	0	0	1
24 F (i)	800	–	–	– (M)
36 F (i)f	800	0	0	0
10 F (ii)m	800	0	0	0
22 F (i)f	800	0	0	1
18 F (ii)f	800	0	0	0
12 F (i)m	800	2	2	0
12 F (ii)f	800	2	1	0
8 F (i)f	800	0	0	1
8 F (ii)m	800	2	0	1
23 F (i)f	1000	1	0	0
3 F (i)m	1000	0	1	0
30 F (i)f	1000	1	1	0
32 F (i)f	1200	0	0	0

Mother—study acquisition number 3–39; epilepsy syndrome F: focal, UC: unclassified. Child—number of pregnancy (i)–(ii); m/f: gender; adverse features 0: none, 1: mild, 2: moderate (M): miscarriage.

(mean ± SD 778 ± 205, coefficient of variation 0.263, $N = 18$). One woman with focal epilepsy (case 24(ii)) prescribed 600 mg per day, had low or undetectable CBZ levels in plasma twice during her second pregnancy. Plasma CBZ was not measured in every patient however.

The outcomes of individual pregnancies in the three assessment areas are shown in Table 3. A moderate adverse outcome in at least one assessment area was found in three offspring.

There was no significant association between adverse outcome and CBZ dose in any assessment area (Table 5). Adverse features were absent or mild in all but the three children who showed moderate dysmorphic features; one only of these children had delayed development. This was moderate and affected mainly speech and motor skills.

Distribution of CBZ dose was different from VPS dose. The variance of VPS dose was significantly greater (variance ratio $F = 5.62$, $P < 0.01$).

Monotherapy with other drugs

The phenytoin (seven cases) and lamotrigine (four cases) monotherapy groups were small. Adverse features were absent or mild. The baby exposed to maternal monotherapy with ethosuximide showed no abnormality.

Polytherapy

The polytherapy group included various combinations of clobazam (CLB), ethosuximide (ESM), gabapentin (GBP), lamotrigine (LTG), phenytoin (PHT), topiramate (TPM) or vigabatrin (VGB) with CBZ or VPS. Individual drug combinations and pregnancy outcomes are summarised in Table 4. Adverse features were absent or mild except in case 42(i) where the woman was receiving VPS 1200 mg per day with LTG 125 mg per day at conception. Spina bifida was seen on anomaly scan and the pregnancy was terminated.

DISCUSSION

Comparison of Tables 2 and 3 shows that an adverse outcome was observed more frequently in association with VPS than with CBZ. Table 2 shows eight offspring exposed to VPS monotherapy, who had a moderate or severe adverse outcome in at least one assessment area. Table 3 by contrast shows only three offspring exposed to CBZ monotherapy with a moderate adverse outcome. The statistical significance of this difference could not be tested formally because the two monotherapy groups were not comparable; they differed in composition (no retrospective cases in the CBZ group and no women with idiopathic generalised epilepsy) and in the distribution of drug doses. A greater risk of adverse outcome with VPS has however also been observed by other investigators.

In a recent study of children with foetal anticonvulsant syndrome most had dysmorphic features and delayed development. The majority (60%) had been exposed to VPS alone compared with only 7% to CBZ[7]. Dysmorphic features in the new-born, which may ‘fade’ with time, are sometimes seen as no more than curiosities but significant association with developmental delay in the present study suggests that they may be markers for neurobehavioral problems, which will emerge later in childhood.

Developmental delay is probably the most serious adverse result of exposure to AED *in utero*. Koch

Table 4: Polytherapy: drugs taken by the mother at conception and severity of the adverse features observed in the child.

Drugs	Dysmorphic features	Developmental delay	Structural anomalies
31 IG (i)f VPS* + CBZ	1	0	0
37 IG (i)m VPS + LTG	1	0	0
42 IG (i) VPS* + LTG	–	–	3 (T)
20 IG (i)m VPS + PHT	1	0	0
12 F (iii) CBZ + CLB	–	–	– (M)
27 F (i)m CBZ + GBP	1	0	0
4 IG (i)m CBZ + ESM	1	1	1
4 IG (ii)f CBZ + ESM	1	0	1
38 F (i)f CBZ + LTG	0	0	1
43 F (i) CBZ + LTG	–	–	– (I)
34 F (i)m CBZ + LTG + TPM	0	0	0
19 F (i) CBZ + PHT + VGB	–	–	– (E)
21 F (i)f CBZ + GBP + VPS	1	1	0

Drugs—CBZ: carbamazepine, CLB: clobazam, ESM: ethosuximide, GBP: gabapentin, LTG: lamotrigine, PHT: phenytoin, TPM: topiramate, VGB: vigabatrin, VPS: sodium valproate (* > 1000 mg per day). Mother—study acquisition number 4–43; epilepsy syndrome F: focal, IG: idiopathic generalised. Child—number of pregnancy (i)–(iii); m/f: gender; adverse features 0: none, 1: mild, 2: moderate, 3: severe, (M): miscarriage, (T): termination, (E): ectopic, (I): intrauterine death.

et a1.[8] conducted a small, controlled, prospective study of pregnancy in women with epilepsy. The frequency of neurological dysfunction at 6 years was highest in the offspring exposed to VPS. Ohtsuka *et al.*[9] in a controlled prospective study also found a relatively high risk of developmental delay in children exposed to VPS.

Adab *et al.*[10] obtained information on 594 children in a retrospective survey of women with epilepsy. The likelihood of additional educational needs was increased in those exposed to VPS *in utero*; the odds ratios relative to children with no AED exposure were 3.4 for VPS monotherapy and 2.5 for polytherapy including VPS. The ratios for children exposed to CBZ and to polytherapy without VPS did not differ significantly from 1.0.

Most AED studies do not assess dysmorphic features or developmental delay but focus on structural anomalies. In a prospective study Canger *et al.*[11] found a higher prevalence of malformations among babies exposed to VPS (10/77; 13%) than to other AED (24/375; 6.4%; chi square, $P < 0.05$). Steegers-Theunissen *et al.*[12] made a controlled, prospective study of 119 pregnancies in women with epilepsy. Major malformations in the offspring of those receiving monotherapy were more common with VPS (3/19) than with CBZ (1/39) but the difference was not significant.

Fairgrieve *et al.*[13] conducted a population based, prospective study in pregnant women with epilepsy. Prevalence of malformations was 20/400 (5%), approximately twice that in the general population. CBZ monotherapy was more frequent than VPS in the ratio of about 3:2. Despite this bias malformations were more common with VPS (11) than with CBZ (6).

Not every investigator has found an adverse outcome more frequently with VPS than with CBZ, however. Samren *et al.*[14] evaluated pooled data from five prospective European studies. Despite finding a significant association between VPS dose and major congenital defect they failed to show a greater risk of defect with VPS than with CBZ.

Our finding of a positive relationship between adverse outcome and VPS dose (Tables 2 and 5) is consistent with published work on structural defect. Such a relationship was reported for spina bifida by Omtzigt *et al.*[15], for major congenital anomalies by Samren *et al.*[14,16], and for congenital malformations in general by Kaneko *et al.*[17]. New studies which could reveal similar dose–response relationships for dysmorphic features and developmental delay are awaited.

The failure to find a dose–response relationship for CBZ in this study (Table 5) may reflect a difference in prescribing rather than an intrinsic difference in toxicity. The narrow spread of CBZ doses (Table 3) decreases the likelihood of finding a dose–response relationship. There was no clinic policy to recommend an upper limit to CBZ dose before conception but the diplopia and ataxia associated with high doses probably create a natural upper limit. The ability of patients by contrast to tolerate relatively high doses of VPS without symptomatic toxicity may therefore create a hazard in pregnancy.

The worst outcomes were seen in the offspring of mothers prescribed VPS at doses above 1000 mg per day (lower half of Table 2 and cases 31(i) and 42(i) in Table 4). This was the only treatment group in which adverse features in any of the three assessment areas were severe. When the offspring exposed to such doses (10 monotherapy, 2 polytherapy) were excluded, the remaining 47 pregnancies showed a relatively low risk of moderate adverse effects and no severely affected cases (Fig. 1b). The ability of three mothers (retrospective cases in Table 2) to have healthy children, after reduction of VPS dose or transfer to other treatment, supports the premise that a high dose of VPS played a major part in the earlier adverse outcome.

Several investigators have reported a high risk of adverse outcome to pregnancy with maternal doses of VPS above 1000 mg per day Samren *et al.*[14]; Omtzigt *et al.*[15]; Kaneko *et al.*[17] and the Guideline Development Group of the Royal College of Physicians of London[2] recommended the avoidance of such doses before conception.

We acknowledge the limitations of the study, which was biased towards poor outcome by inclusion of patients with difficult-to-manage epilepsy and with adverse outcomes to earlier pregnancies. The absence of

Table 5: Association between adverse outcome to pregnancy and dose of antiepileptic drug prescribed before conception.

	Dysmorphic features	Developmental delay	Structural anomalies
Carbamazepine			
Coefficient	0.036	0.213	−0.238
Probability *P*	0.891	0.412	0.358
Number of cases	17	17	17
Sodium valproate			
Coefficient	0.645	0.459	0.535
Probability *P*	0.005	0.064	0.018
Number of cases	17	17	19

Coefficient: Spearman rank correlation coefficient, probability: significant at $P < 0.05$ (two tailed).

controls and the awareness of maternal drug history by the doctor assessing the children were also weaknesses.

There were also several opportunities for the confounding of relevant variables. For example idiopathic generalised epilepsies, which are likely to have a genetic basis, were more often treated with VPS than with CBZ. Similarly, patients counselled before conception were more likely to receive not only low dose monotherapy but also folic acid.

CONCLUSION

Despite its limitations the results of this study add to the growing body of evidence that VPS in pregnancy at doses above 1000 mg per day carries a particular risk of adverse outcome. Sodium valproate at such doses should therefore be avoided when pregnancy is likely.

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